Mechanisms of virus-induced immune suppression

Mark A. Wainberg,* PhD
Elaine L. Mills,† MD

The recent demonstration that the acquired immune deficiency syndrome (AIDS) is caused by a retrovirus that affects humans has given rise to widespread concern about the immunosuppressive properties of viruses in general. A wide variety of viruses have been shown to be able to compromise immune function. Sometimes immunosuppression results from the pathologic processes that viruses are able to induce. In other instances virus-induced immune derangements may themselves be responsible for the onset of pathologic change. In some cases a single infectious viral agent may be able to modulate several immunologic mechanisms simultaneously. This review discusses some of the various complex mechanisms through which viral infections can alter the function of the immune system.

La preuve, faite récemment, que le syndrome immunodéficitaire acquis (SIDA) est causé par un rétrovirus pathogène pour l'homme a suscité partout des inquiétudes quant au rôle immunosuppresseur des virus dans leur ensemble. Ce rôle existe pour un grand nombre d'entre eux apparte-nant à divers genres. Dans certains cas, la défense immunitaire est compromise du fait des processus pathologiques mis en route par le virus. D'autres fois, c'est la perturbation qu'il amène dans les défenses immunitaires qui détermine les altérations tissulaires. Un seul virus agit parfois en même temps sur plusieurs composantes des moyens de défense. L'auteur passe en revue quelques-uns des mécanismes immunitaires complexes de modification de la fonction immunitaire par l'infection virale.

From *the Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, *†the Montreal Children's Hospital, and the departments of *Microbiology and Immunology and †Pediatrics, McGill University, Montreal

Reprint requests to: Dr. Mark A. Wainberg, Sir Mortimer B. Davis Jewish General Hospital, 3755 Côte St. Catherine Rd., Montreal, PQ H3T 1E2

The first recorded observation of virus-induced immunosuppression was made in 1908 by the German physician Clemens von Pirquet.[1] Patients suffering from infection by measles virus, he said, had a diminished capacity to mount delayed cutaneous hypersensitivity (DCH) reactions to tuberculin antigen. In von Pirquet's day the tuberculin skin test was considered to give a reliable indication of the body's overall defensive capability. In children and young adults who had not been sensitized against *Mycobacterium tuberculosis* antigens, of course, the test often gave negative results, so his analysis may not have been as scientifically correct as we might expect today.

Although his knowledge and understanding of measles was limited, von Pirquet had seen that exposure to a "filterable", non-free-living infectious entity could lead not only to the disease state known as measles but also to a variety of other types of infectious processes that we would today consider to be opportunistic disease. His classic paper on skin test responsiveness in measles patients is justly cited as an important original contribution to the field of virus-induced immunosuppression.

Since von Pirquet's time there have been many other reports of immunosuppression following acute viral illnesses, such as influenza.[2,3] By impairing the immune system viral infections can predispose the patient to other, more serious illnesses of bacterial, fungal, parasitic or even viral origin. There is controversy in the literature as to whether immune suppression can also weaken the defence mechanisms that guard against neoplasia, but viruses could enhance the development of cancer by interfering with the natural-killer (NK)-cell system. NK cells constitute a subpopulation of lymphocytes that are able to kill not only virus-infected target cells but also tumour cells, and should viral infection result in decreased NK-cell function for any length of time, then host defences against both viral infection and neoplastic development would suffer.

Specific antiviral reactivity on the part of lymphocytes has been demonstrated in a large number of systems, as tested by in-vitro assay. However, it appears that virus particles can also exert profound inhibitory effects. Viral infections can diminish the ability of lymphocytes to be stimulated by various antigens and mitogens. This means that viruses can impair the ability of the immune system to recognize bacterial and other pathogens as foreign and to react against them. Both specific antibody production by B lymphocytes and the ability of T lymphocytes to mediate direct cyto-

toxicity, or killing, of virus-infected or cancer-cell targets can be suppressed.

A wide variety of viral illnesses can predispose to bacterial disease. Most notably, influenza epidemics have classically been associated with increased mortality from pulmonary and systemic infections of multiple origin.[4] The organisms responsible for such secondary or opportunistic disease include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Staphylococcus aureus*.[5,6] In rats, too, infection by influenza B virus augments the rate of colonization by *H. influenzae* and reduces the number of these organisms needed to produce meningitis.[7]

In children previously infected by respiratory syncytial virus (RSV) the incidence of otitis media can be considerably increased.[8] Why previous infection with RSV should be a greater risk factor than previous respiratory tract infection with other viruses is not known, but there is evidence that RSV can attack the lining of the middle ear;[9] this tissue may therefore be predisposed to bacterial colonization. Bacteria may adhere nonspecifically to tissue that has been damaged by viral injury or even by the sort of injury that is caused by cigarette smoke. Pharyngeal cells from volunteers who had been experimentally infected with influenza virus were reported to bind bacteria more efficiently than cells of uninfected control subjects.[10]

Bacterial infection frequently supersedes viral disease because there has been an alteration in host defences. In cows functional defects have been reported in circulating lymphocytes, macrophages and polymorphonuclear neutrophils from 4 to 7 days after infection with bovine herpesvirus, a time when virus replication in the nasal passages apparently peaks.[11] This impairment of immune-system cells may contribute significantly to the lungs' enhanced susceptibility to bacterial colonization.

In humans infected with influenza virus, as well as in a number of animal models, the function of alveolar macrophages is severely compromised. The ability of these cells to mediate nonspecific phagocytosis of bacterial cells and other foreign materials is frequently impaired.[12,13] More importantly, these cells often are unable to participate in the phagocytosis that is mediated by receptors for Fc (the crystallizable fragment of IgG) at the macrophage surface.[14] In this type of reaction the macrophages use the antibacterial antibody on their surfaces to recognize and react against the bacteria.

A number of studies have focused on the mechanisms whereby viruses impair the function of phagocytic cells. Ingestion of virus particles usually leads to an oxidative burst and superoxide production in the neutrophils and monocytes of humans.[15] In the neutrophils of chinchillas the respiratory burst, bactericidal activity and chemotaxis became depressed 4 to 8 days after intranasal inoculation of the animals with influenza virus.[16] Phagosome–lysosome fusion may also be impaired following viral infection, and the extracellular release of myeloperoxidase may be compromised. Infection with influenza virus can inhibit the phagosome–lysosome fusion that would normally destroy staphylococci contained in the phagosomes.[17]

Effects of viral infection on immune function

Study of the mechanisms of immunosuppression have yielded a variety of sometimes contradictory results. This situation no doubt stems, at least partly, from the great variety of virus particles studied and model systems, both in-vitro and in-vivo, used.

In certain rare instances immune function is actually enhanced following infection by an immunosuppressive virus; this, however, is only transient. Acute infection of mouse B cells by lactic-dehydrogenase-elevating (LDH) virus, for example, dramatically increased the cells' ability to produce antibody against sheep red blood cells.[18] Responsiveness subsequently became inhibited as the disease passed into a chronic stage.

It has been suggested that the early stimulation of antibody synthesis may reflect a virally fostered expansion of the responding B-cell population;[19] Epstein–Barr virus (EBV) can have this result in humans. Minato and Katsura[20] demonstrated that vesicular stomatitis virus can augment antibody production by growing selectively in certain subpopulations of suppressor T cells, which are then eliminated by lysis.

More frequently, viral infection leads to lymphocytopenia. In several classic experiments the Woodruffs[3] showed that infection with Newcastle disease virus (NDV) significantly reduced the circulation of T cells in the body, an effect that may conceivably play a role in the onset of lymphocytopenia. Such a decrease in the numbers of circulating lymphocytes might account for McFarland's report of a reduction in the B cells' ability to make specific antibody and a depression of T-helper-cell function in mice infected by measles virus.[21] In addition, a decrease in the numbers of total lymphocytes may explain the fact that infection of mice with any of several viruses, including NDV and LDH virus, can give rise to prolongation of skin allograft survival.[3]

Evidence for the involvement of suppressor-cell activity following viral infection has come from a variety of models. For example, impairment of the proliferative response to mitogens and of immune function by suppressor cells has been reported for the spleen cells of mice and chickens infected by retroviruses.[22,23] Other viruses that have been known to result in the predominance of suppressor-cell functions are measles virus,[24] herpes simplex virus (HSV)[25] and reovirus.[26] In some cases, including reovirus type III, suppressor T cells can be generated by exposure to a single viral component, such as viral hemagglutinin.[27] Such suppressor cells may sometimes be able to inhibit the response to a variety of viral agents, while in other instances the suppression is antigen-specific.

Working with the Friend leukemia virus (FLV) model, Kumar and Bennett[28] showed that active infection generated a population of splenic suppressor cells that had the ability to regulate in-vitro responses to lectin. Large numbers of these cells may govern the kinetics of the appearance of FLV-specific cytotoxic T lymphocytes, which seem to be necessary for recovery from the infection.[29] In addition, these inves-

tigators showed that the virus had to be fully infective for the suppression of T- and B-cell responses to mitogens. It has been the experience of most investigators that infection of the lymphoid cells is a prerequisite for the abrogation of immune function.

There is little doubt that complex stimulatory and inhibitory interactions underlie the relation between host defence mechanisms and viruses.

Effects of viral coincubation on lymphocyte function

Our laboratory has been involved in the field of virus–lymphocyte interaction for many years and was one of the first to show that coincubation of viruses and lymphocytes could impair the ability of the latter to respond to antigenic and mitogenic stimuli. In many cases we were able to show that these interactions were in a sense nonspecific, or at least infection-independent. For instance, we demonstrated that the responsiveness of not only avian but also human and mouse lymphocytes could be inhibited by avian retroviruses.[30] This is noteworthy because human and mouse cells lack the genetically coded receptors normally required for attachment and penetration by avian retroviruses. We also obtained a suppression of lymphocyte responsiveness with both ultraviolet-light-inactivated and live virus; individual viral proteins, however, were unable to produce the same inhibitory effects as intact virus particles.[31] Observations of this kind, also made by other groups,[27,32] have led us to believe that certain types of viruses may be structured in such a way as to play a role in immune regulation and that structural integrity of the virus particle is essential for this to happen.

Viral abrogation of the lymphocyte response to mitogens, we find, is due to neither the displacement of bound lectin at the lymphocyte surface nor any apparent virus-associated enzyme activity.[31] Rather, viruses cause adherent cells (mostly macrophages) to produce a soluble inhibitory factor, now thought to be prostaglandin. This factor can be used in transfer experiments to inhibit the proliferation of freshly obtained cells. The addition of indomethacin inhibits the production or release of this factor and also leads to increased lymphocyte responsiveness in the presence of viruses, which supports the notion that a prostaglandin is involved.

When poliovirus was used to interfere directly with in-vitro mitogenesis the immunosuppressive effect required the presence of both macrophages and live virus.[33] The investigators concluded that poliovirus inhibits the mitogenesis of lymphocytes by infecting macrophages and thereby suppressing their enhancing effect. A similar scenario was drawn by Roberts and Steigbigel[34] on the basis of experiments involving peripheral lymphocytes and macrophages from humans plus influenza virus. From reconstitution experiments involving infected and uninfected macrophages these workers concluded that viral infection has no adverse effect on lymphocyte responsiveness per se but, rather, that infected macrophages were responsible for the observed failure of coincubated lymphocytes to undergo lectin- and alloantigen-driven mitogenesis.

In other cases it remains clear that the use of live virus is necessary to obtain an inhibitory effect. Lucas and coworkers[35] observed that coincubation of peripheral lymphocytes from humans and live but not antibody-neutralized measles virus interfered dramatically with responsiveness to both phytohemagglutinin and pokeweed mitogen. Subsequent experiments showed that monocytes were probably not involved. More recently, Casali and colleagues[36] showed that coincubation of lymphocytes and live measles virus led to a diminution of both NK-cell activity and the ability to produce immunoglobulin, even though neither progeny virus nor viral antigen was expressed under the circumstances tested. The results reaffirm that viruses can profoundly affect the function of lymphoid cells without necessarily causing apparent infection or cytotoxicity.

During the past several years our laboratory has investigated other mechanisms whereby viruses impede immune function. In work since confirmed by other investigators in other models[37] we showed that several types of virus particles, especially retroviruses, can impair the proliferative responsiveness of human lymphocytes to mitogens and antigens by interfering with the synthesis of T-cell growth factor (TCGF).[38] TCGF is a lymphokine produced by helper T cells; it signals all T cells to proliferate and is released following activation of the helper cells by antigens or mitogens.[39] Interference with the generation of TCGF leads to a failure of lymphocytes to multiply (Fig. 1). The addition of TCGF to cultures of lymphocytes whose responsiveness to

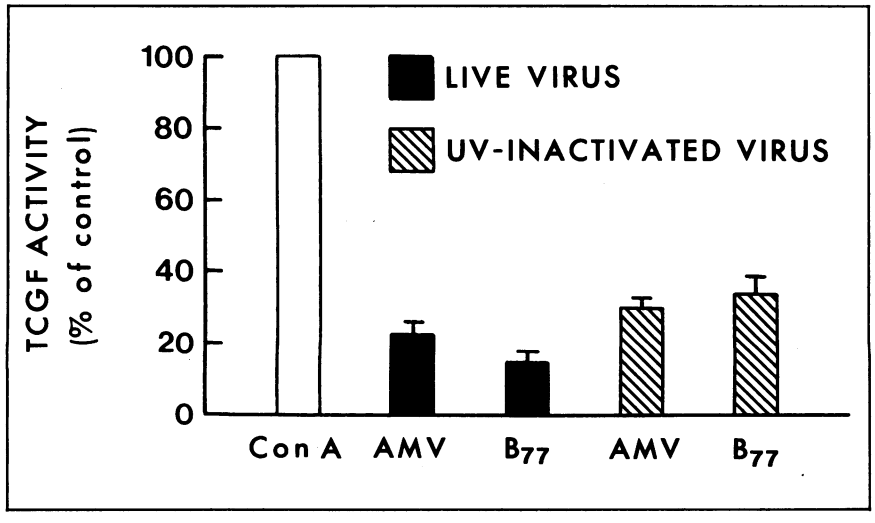

Fig. 1—Effect of coincubation of lymphocytes from humans and live or ultraviolet-light (UV)-inactivated viruses on production of T-cell growth factor (TCGF) following stimulation by concanavalin A (Con A), a T-cell mitogen. Avian retroviruses AMV and B_{77} are able to inhibit production of TCGF through mechanisms explained in the text.

lectins had been inhibited by coincubation with virus restores cellular blastogenesis and proliferation (Fig. 2). Both HSV and avian retroviruses can also complex directly with TCGF and make it unavailable to the lymphocytes.[40] Thus, viruses may be able to block the action of TCGF on target cells through a variety of mechanisms.

Experiments on viral inhibition of lymphocyte mitogenesis now extend into clinical areas. The results in breast-cancer patients who had received adjuvant chemotherapy indicate not only that less virus is required to achieve significant levels of inhibition than in healthy controls but also that exogenous TCGF is less effective at restoring responsiveness.[41]

Individuals with frequent recurrences of lesions caused by HSV, we find, are similarly distinguished from individuals with either few recurrences or no disease. Lymphocytes from people in the first group are more susceptible to viral inhibition of mitogenesis and less responsive to TCGF than are cells from the other individuals. Yet almost all herpes sufferers have demonstrable anti-HSV cellular and humoral immunity. We have therefore postulated that the ability of HSV to abrogate the proliferative responsiveness of lymphocytes may be important in the microenvironment of the recurrent lesions themselves.[42]

In a mouse model we have found that retroviruses can apparently activate the production of prostaglandins, which leads to a curtailment of interleukin-1 (IL-1) as well as TCGF production. This finding is consistent with the demonstration by other workers that the synthesis or release of IL-1 is necessary for the production of TCGF.[43] Indeed, we have further shown that the addition of exogenous IL-1 activity to cultures of lymphocytes coincubated with virus partially restores lectin-driven cellular proliferation and causes the synthesis of some TCGF. The schema of nonspecific viral inhibition of lymphocyte mitogenesis is depicted in Fig. 3.

Cytomegalovirus (CMV) and EBV

CMV is a herpesvirus that has been shown to be potently immunosuppressive. Most individuals become infected by this agent and convert to seropositivity by the time they reach the age of 30 years, but the disease is usually subclinical. However, CMV infections do result in considerable morbidity and mortality in recipients of bone-marrow and renal allografts.[44-46] Among these and other immunocompromised individuals the infections may be either primary or reactivations of latent infections. These CMV infections are frequently followed by opportunistic infections of bacterial, fungal or parasitic origin,[46,47] and a fatal outcome is not uncommon under such circumstances. The fact that immunocompromised patients are prone to infection with CMV, of course, reflects an inability of the immune and other natural defence systems to deal with this virus in the usual way. The occurrence of opportunistic disease in a high proportion of cases is indicative of the further weakening of the immune system that is brought about by CMV infection. Lymphocyte responsiveness to specific antigens and to B- and T-cell mitogens can be depressed for up to 60 days following the development of CMV mononucleosis.[48] In animal models depression of humoral and cell-mediated immunity follows infection by CMV.[49] Moreover, CMV-infected macrophages display impaired ability to engulf bacterial cells. CMV and several types of bacteria can act synergistically in mice, causing death.[49] Thus, in immunosuppressed individuals CMV disease is both the result of an underlying immunodeficiency and a factor predisposing to more severe opportunistic infection.

EBV is another member of the herpesvirus group that is associated with immunosuppression and also with lymphoproliferative disorders. This virus is classically associated with infectious mononucleosis (IM), a disease that reflects EBV's ability to transform B lymphocytes. Normally the body's defence mechanisms manage to cope with the resultant B-cell proliferation. In some situations, however, life-threatening lymphoproliferative disorders occur and result in severely weakened overall host immunity and susceptibility to opportunistic disease. The X-linked lymphoproliferative syndrome (XLP) is the prototype of this disorder.[50]

In EBV-induced lymphoproliferative disease the immunologic mechanisms that normally provide surveillance against transformed B cells in EBV infections — NK cells, specific anti-EBV antibody, interferon and cytotoxic T lymphocytes — do not

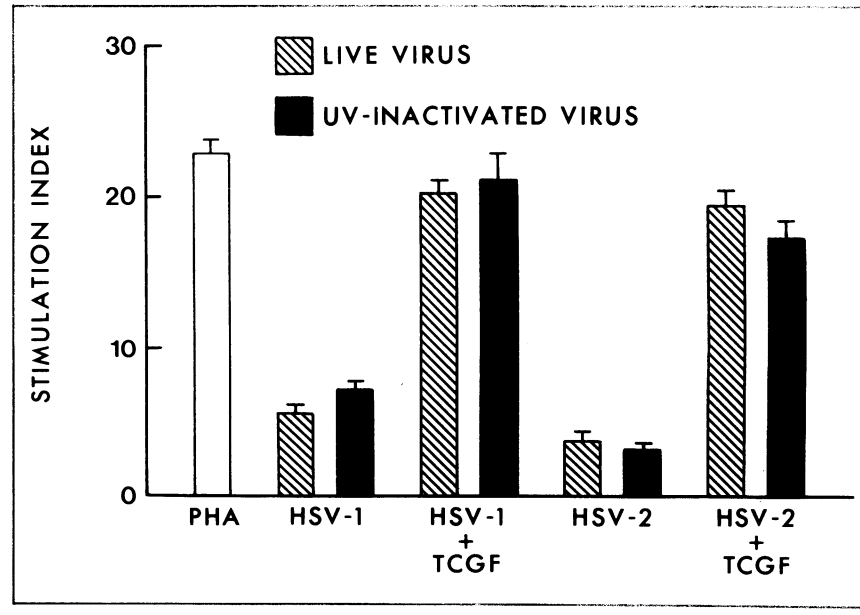

Fig. 2—Restoration of responsiveness of lymphocytes from humans to the cell mitogen phytohemagglutinin (PHA) by the addition of TCGF. Herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) were used to inhibit mitogenesis. Both viruses impeded lymphocyte responsiveness to PHA regardless of whether they had been UV-inactivated.

function adequately. Moreover, progress of the disease can rapidly lead to permanent activation of suppressor T cells and decreased levels of NK-cell activity.[51] In many cases lymphomas may develop. EBV-related lymphoproliferative disorders have been reported in patients who had undergone immunosuppressive therapy following allograft procedures and in patients with the acquired immune deficiency syndrome (AIDS).[52]

Human T-lymphotropic viruses and AIDS

That the field of virus-induced immune suppression has been thrust into the public eye is largely a consequence of the rapid appearance of AIDS in North America. AIDS is caused by a retrovirus, variously referred to as the lymphadenopathy-associated virus (LAV)[53] or the human T-lymphotropic virus, type III (HTLV-III).[54] It is clear that this agent is a very unusual retrovirus.

Many retroviruses are able to transform susceptible cells quite rapidly, after only 24 to 72 hours, causing them to acquire a neoplastic phenotype. These same retroviruses are usually also able to cause tumours after short latent periods in susceptible hosts. These abilities ordinarily depend on the presence within the viral genome of a segment called the *onc* or transforming gene,[55] which LAV/HTLV-III does not have. Other retroviruses that lack this gene generally cannot rapidly induce tumours in animals, nor can they transform cells in tissue culture, although they do replicate in these cells without killing them and frequently can cause certain types of leukemias and lymphomas in animals after long latent periods.[56]

AIDS is unique among retroviruses for another reason: exposure often results in the death of the infected cells. Since these cells are almost exclusively helper T cells, T-helper-cell function in afflicted individuals is almost nonexistent.[57] Thus, LAV/HTLV-III appears to be acting in the fashion of a classic life-threatening viral agent by attacking and destroying a population of cells whose survival and function are crucial to life. In this context, therefore, it is extremely relevant that LAV/HTLV-III attaches to helper T cells through specific receptor structures located at the cell surface.[58,59] This structure, called the T4 antigen, is recognized by mouse monoclonal antibodies specifically directed against it. In this sense AIDS is not typical of virus-induced immunosuppressive disorders, which generally involve an upset in immune regulation, with the potential for ultimate recovery. In AIDS the destruction of an essential component of the immune system makes the problem far more serious. For this reason it is important that public health measures be strengthened to limit the spread of this virus.

Other viral agents may apparently act in concert with LAV/HTLV-III to produce AIDS. CMV, which can act like a mitogen, stimulating the division of helper T cells, is thought to cause the proliferation of these cells when they are infected by LAV/HTLV-III, so that this agent becomes disseminated throughout the immune system. In this scenario CMV would thus convert a helper T cell that had been latently infected by LAV/HTLV-III into an efficient producer of progeny virus, and the AIDS virus would spread to other previously uninfected T cells.

It is becoming apparent that large numbers of people in our society are seropositive for LAV/HTLV-III. In certain groups at high risk for AIDS, such as homosexuals, the rate of seropositivity has been reported to vary between 35% and 65%.[60,61] This does not mean that AIDS will develop in all seropositive individuals. None the less, seropositivity is evidence of infection by LAV/HTLV-III. It is therefore important to identify seropositive individuals, because they not only may be at highest risk for the development of AIDS but also could transmit the virus to others. We hope that a test to detect neutralizing antibody to LAV/HTLV-III will soon be developed. We might find that in some seropositive individuals the AIDS virus has, in fact, been eliminated from their bodies owing to a successful antiviral immune

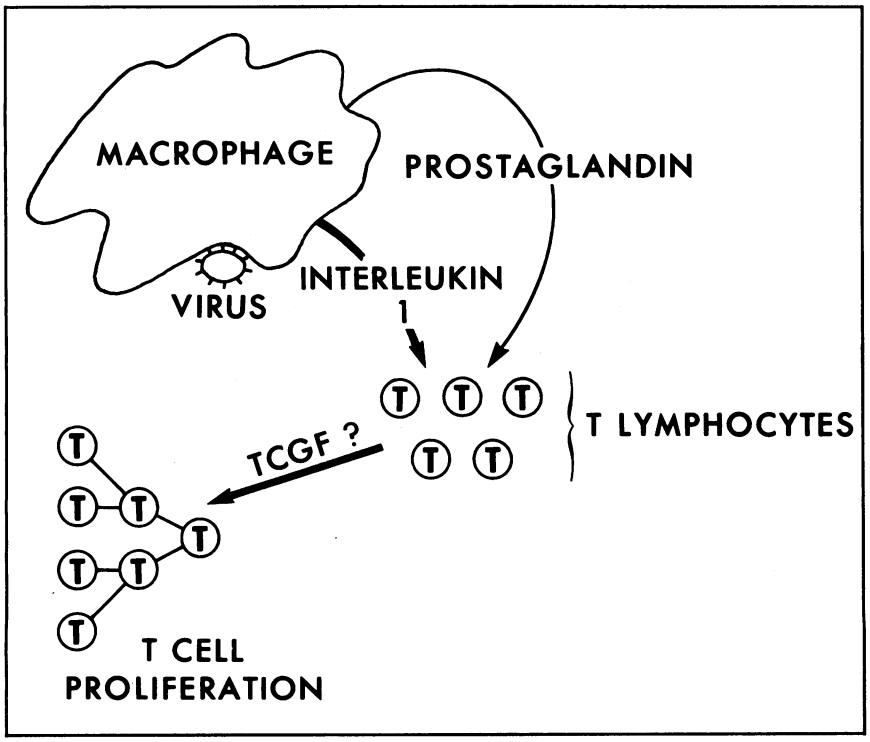

Fig. 3—Under normal circumstances macrophages stimulated by activated T cells produce interleukin-1 (IL-1), which causes certain populations of helper T cells to produce TCGF. TCGF acts as a necessary second signal for T-cell proliferation in response to antigens or mitogens. Some viruses, however, cause macrophages to produce prostaglandins that limit IL-1 production. The production of TCGF is thereby diminished, and this prevents adequate T-cell proliferation.

response, whereas in others antibodies have not succeeded in neutralizing the viral agent. Identification of LAV/HTLV-III carriers is clearly a public health priority at this time.

Summary

The mechanisms whereby viruses may interfere with host defence mechanisms generally and the immune system in particular are probably as varied as the viral agents themselves. Some viruses infect and kill cells such as helper T lymphocytes that are crucial in immune defence. Other viruses interrupt cascades of interconnected events and affect several facets of immune responsiveness at once. The end result is often serious, if not life-threatening, opportunistic disease. We must endeavour to further delineate the mechanisms of virus-mediated immune suppression so as to better develop worthwhile approaches of immunologic intervention.

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